REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

Claims 1-20 have been cancelled. New claims 21-29 have been introduced. Support for the amendments to the claims can be found in the claims as originally filed and in the specification. No new matter has been introduced by the instant amendments.

The specification stands objected to because it fails to cross-note the international application upon which the is application's priority is based.

The specification has been amended to include, on page 1, a cross-reference to related applications properly identifying the instant application as a §371 of copending PCT/JP00/0582, filed August 21, 2000.

The drawings stand objected to because they fail to refer to figure numbers and reference characters in English.

Applicants, at the time of national entry, filed drawings in which the figure numbers and reference characters were translated into English. A copy of the originally filed drawings are enclosed herewith.

The Office action indicates that a concise explanation of the relevance was not provided for certain non-English language documents submitted with the IDS filed February 28, 2003.

We provide the following description of JP 06-338730 and the publication entitled "High-Density Culture Of Hepatocytes For Use As A Bioartificial Liver".

The reference titled "High-Density Culture Of Hepatocytes For Use As A Bioartificial Liver" relates to the use of packed-bed type reactors. Applicants provide an English language summary of the reference.

Japanese patent publication JP 06-38730 is directed to a carrier, not a reactor, which may be used in the present invention. An English language translation of the summary and claims 1 and 2 are provided herewith.

Thus, the documents filed with the information dislcosure statement on February 28, 2003 fully comply with 37 CFR 1.98, including the explanation requirment of 1.98(a)(3). Applicants request that the form PTO-1449 listing the two above discussed documents be initialed to reflect the submission of a concise explanation of the documents relevance. A copy of the original PTO-1449 is enclosed for the convenience of the examiner in initialing the previously uninitialed documents.

Claims 1, 2, 4, 6-11, 15, 16, and 18 were rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of which applicant regards as the invention.

Claims 21-29, as currently presented, are fully compliant with the requirements of 35 U.S.C. §112, including the definiteness requirements of §112, second paragraph. Applicants request withdrawal of the rejection.

Claims 1, 2, 4, 6-8, 15, 16, and 18 stand rejected under 35 U.S.C §103(a) as being allegedly unpatentable over Seipp in view of Takeshita.

Claims 1, 2, 4, 6-8, 15, 16, and 18 stand rejected under 35 U.S.C §103(a) as being allegedly unpatentable over Seipp in view of Kawada.

For the sake of brevity, the two §103 rejections are addressed in combination. Such a combined response is considered appropriate because *inter alia* each of the rejections relies on Seipp as the sole or primary citation. Each of the rejections is traversed.

The rejection is traversed. The cited documents, even in combination, do not teach or suggest Applicant's claimed invention in any manner sufficient to sustain a rejection under 35 USC §103.

It is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references to make the claimed invention, nor is there a reasonable expectation of success. The cited references clearly do not teach or suggest the features of the present invention.

For instance, new claim 21 recites a method for proliferating a hepatitis C virus, comprising immobilizing human hepatocyte cells on a porous carrier in a culture vessel by introducing a continuous stream of liquid medium comprising the human hepatocyte into the culture vessel. The immobilized hepatocyte cells are subsequently infected with a hepatitis C virus, an infectious clone RNA thereof, or a combination thereof. The method further provides for a step of proliferating the hepatitis C virus in the infected

immobilized hepatocyte cells in a continuous stream of culture medium. These features of the present invention are not taught or suggested by the cited references, even in combination. In particular, no combination of the cited references teaches or suggests proliferating infected hepatocytes in a continuous stream of a culture medium.

Moreover, one of ordinary skill in the art would not have a reasonable expectation of obtaining level of increased proliferation or temporal stability of proliferation obtained by the claimed methods from any combination of Seipp, Takeshita, and/or Kawada.

As the reference is understood, Seipp merely recites a rudimentary method for obtaining viruses by using host cells for proliferation. More particularly, Seipp teaches a method of proliferating HCV by using infected human hepatocyte cells which are not immobilized on a porous particulate carrier and are not placed in a continuous stream of liquid culture.

As the reference is understood, Seipp teaches inoculating cells by a static dose of viruses and then culturing the cell-virus mixture for a set number of days in a static culture media. Thus, Seipp neither teaches nor suggests a method of proliferating hepatitis C virus in which the host cells are infected with virus introduced into a continuous stream of liquid culture media. The Seipp methods provide a proliferation level of HCV which is barely detectable by RT-PCR and is not constant over several generations. Thus, Seipp does not teach a stable method of proliferating HCV.

As the Office Action is understood, the position is taken that either of Takeshita's or Kawada's methods of culturing hepatocyte cells are suitable for use in Seipp's rudimentary methods of proliferating viruses.

It is submitted, however, that neither Takeshita nor Kawada overcome the limitations of the Seipp disclosure. Neither Takeshita nor Kawada teaches or suggest

proliferating a HCV in immobilized cells placed in a continuous stream of culture medium.

As the references are understood, Takeshita and Kawada merely recite different culture vessels and methods of culturing hepatocyte cells in said vessels.

Neither Takeshita or Kawada teach or suggest methods of infecting the cultured hepatocytes with a virus or methods of culturing infected hepatocytes to proliferate the infecting virus. Neither Takeshita nor Kawada suggest that conducting the Seipp HCV proliferation method in the culture vessels of Takeshita or Kawada would provide increased proliferation levels or increased proliferation rate stability. Thus, even if the cited references are combined, one of ordinary skill in the art would not have had a reasonable expectation of obtaining the increased level of HCV proliferation obtained by the instant method in view of the barely detectable levels of HCV obtained in the Seipp method.

In contrast, the methods provided by the claimed invention provide several orders of magnitude more proliferated HCV compared to the Seipp methods. The proliferation methods of the invention further provide improved stability (e.g., stable proliferation for 100 days) and detectable levels of HCV protein. See, for example section (5) of Example 1, section (2) of Example 2 and Figure 4 of the application as filed.

The methods of the instant invention provide proliferation of HCV by infection with either HCV, an infectious clone RNA thereof or a mixture thereof. See, the specification at sections (2) and (4) of Example 2 and Figure 5.

No combination of Seipp, Takeshita and/or Kawada teach method of proliferating hepatitis C virus including a process step of proliferating HCV in infected immobilized hepatocytes in a continuous stream of culture medium as provided by new claims 21 and 25. Thus, their combination cannot teach the claimed method. Furthermore, given

the rudimentary nature of the proliferating method recited by Seipp, the skilled artisan would not have been be motivated to combine the references in the first place and would not have had a reasonable expectation of success.

In view thereof, reconsideration and withdrawal of the §103 rejection are requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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